

Soluble fibers are thought to lower serum cholesterol levels by binding bile salts in the intestine. In response, the liver increases its conversion of cholesterol to bile acids. The depletion of the liver cholesterol content stimulates a synthesis of LDL receptors, a primary mechanism for removing LDL cholesterol from serum. The addition of soluble fibers such as oat bran to a low-fat, low-cholesterol diet may be an inexpensive nonpharmacologic way to help reduce serum cholesterol levels.

Another dietary theory proposes that the type of fat ingested may play a more important role in determining serum cholesterol levels than the amount. People in Mediterranean countries who eat a diet high in total, predominantly monounsaturated fat have a low incidence of coronary artery disease. Short-term studies have compared the effects on serum lipids of volunteers who ingested diets high in total and monounsaturated fat, high in total and saturated fat, or low in total fat. The high-monounsaturated-fat and low-fat diets had similar effects in lowering total and LDL cholesterol levels when compared with the high-saturated-fat diet. These study diets differed from Mediterranean diets. They used liquid formulas low in complex carbohydrates, high in glucose, and high in safflower oils rather than olive oil. The long-term effects on serum lipids of diets high in total and monounsaturated fat have not been studied. It is premature to conclude that such a diet will lower the incidence of coronary artery disease. The current recommendations for North American adults include a small increase in monounsaturated fat consumption to partially replace decreased saturated fat intake.

What about fish oils, the ω -3 fatty acids? Pharmaceutical sales of fish oil capsules have dramatically increased. Interest developed when it was noted that coastal Eskimos and other populations whose diets are rich in these substances have a low incidence of coronary artery disease. Even in large quantities, ω -3 fatty acids cause only a modest decrease in serum cholesterol levels; they primarily lower triglyceride levels. They also decrease platelet aggregation and the synthesis of thromboxane A_2 , factors implicated in the pathogenesis of atherosclerosis.

Whether ingesting ω -3 fatty acids will reduce the incidence of coronary artery disease is unknown. Patients should be informed that the typical North American diet, high in saturated fat, cannot be turned into an "Eskimo diet" by adding fish oil capsules. Eskimos have a high incidence of stroke, and there is concern this may be related to the hemostatic alterations of ω -3 fatty acids. To match the Eskimo diet in ω -3 fatty acids would require using as many as 30 to 60 capsules per day, with an average daily cost of \$10. The use of fish oil capsules is not recommended. Epidemiologic evidence suggests that the frequent consumption of fish, whether high or low in ω -3 fatty acids, is associated with a decreased risk of coronary artery disease. Fish can provide a useful substitute for meat high in saturated fat.

CONNIE WHITESIDE, MD
Sacramento, California

REFERENCES

- The Expert Panel: Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988; 148:36-69
- Gold KV, Davidson DM: Oat bran as a cholesterol-reducing dietary adjunct in a young, healthy population. *West J Med* 1988; 148:299-302
- Grundey SM: Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. *N Engl J Med* 1986; 314:745-748

Leaf A, Weber PC: Cardiovascular effects of n-3 fatty acids. *N Engl J Med* 1988; 318:549-557

Recent Advances in Diagnosis and Treatment of Acute Pancreatitis

ACUTE PANCREATITIS is a commonly encountered clinical disorder. In the United States, alcohol abuse and biliary tract disease account for the vast majority of cases. Morbidity and death related to pancreatitis are largely confined to patients with severe necrotizing disease, which accounts for 10% to 18% of cases.

The diagnosis of pancreatitis is made clinically because histologic examination of the gland is not readily available. The clinical diagnosis may be supplemented or supported by laboratory or radiographic evidence. Efforts to improve either the sensitivity or specificity of the diagnosis with specific enzyme or isoenzyme measurements have been largely unsuccessful.

Although diagnostic imaging of the gland may be confirmatory, both ultrasonograms and computed tomograms may be normal in as many as 15% to 20% of patients with acute pancreatitis. The most useful role of computed tomography is in its ability to provide prognostic information and identify complications—abscess or pseudocyst—of pancreatitis. The use of magnetic resonance imaging in acute pancreatitis remains a research tool. Its poor spatial resolution makes it unreliable in differentiating inflammation from necrosis and other pancreatic abnormalities.

The treatment of acute pancreatitis is primarily supportive because most cases are of mild or moderate severity and have a universally good prognosis. Such patients need only be supported with fluid resuscitation and adequate analgesia. Nasogastric suction, H_2 -receptor blockers, atropine, glucagon, aprotinin, and antibiotics have all proved ineffective in improving the outcome in patients with mild to moderate disease, and their use is not recommended.

Early morbidity and death in pancreatitis are related to cardiopulmonary collapse and renal failure, which occur in patients with severe necrotizing or hemorrhagic pancreatitis. Although clinical trials of the use of peritoneal lavage have failed to show an improvement in mortality, lavage may offer a means of support for those with cardiovascular collapse.

Although early death may not be avoided, late mortality may be prevented. Death after 10 to 14 days occurs as the result of septic complications. Controlled trials have shown that the prophylactic use of antibiotics is of no benefit in improving outcome, but these studies are flawed in that the population studied was at low risk (nonsevere pancreatitis). A growing body of literature suggests that bacterial contamination occurs more frequently—in 40% of cases—and earlier (seven to ten days) than previously assumed in patients with severe necrotizing pancreatitis. In this population, antibiotic prophylaxis may be beneficial.

Unfortunately, a case of sterile necrosis cannot be clinically differentiated from a case of infected necrosis. In both, patients may have fever, leukocytosis, and a clinically deteriorating course. Computed tomography-guided aspiration of necrotic areas or liquid collections has proved to be a reliable means of detecting or excluding bacterial infection. The presence of organisms on a Gram's stain or a culture requires either aggressive surgical debridement or radiologic catheter drainage.

Using an aggressive aspiration approach in patients with

severe necrotizing pancreatitis and early operative or catheter drainage may result in improved survival rates. The use of prophylactic antibiotics in these patients should be evaluated by a controlled trial.

M. BRIAN FENNERTY, MD
Tucson

REFERENCES

- Beger HG, Bittner R, Block S, et al: Bacterial contamination of pancreatic necrosis—A prospective clinical study. *Gastroenterology* 1986; 91:433-438
- Gerzof SG, Banks PA, Robbins AH, et al: Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology* 1987; 93:1315-1320
- Nordstgaard AG, Wilson SE, Williams RA: Early computerized tomography as a predictor of outcome in acute pancreatitis. *Am J Surg* 1986; 152:127-132
- Ventrucci M, Pezzilli R, Gullo L, et al: Role of serum pancreatic enzyme assays in diagnosis of pancreatic disease. *Dig Dis Sci* 1989; 34:39-45

Misoprostol Therapy for Patients Taking Nonsteroidal Anti-inflammatory Drugs

GASTROPATHY INDUCED BY the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a major complication of these widely prescribed drugs. Patients at highest risk for gastropathy are those on long-term NSAID therapy, including the elderly, arthritic patients, and those with a history of abdominal pain or gastric intolerance to NSAIDs. The spectrum of gastropathy includes mucosal hemorrhages or erosions, gastric ulcer—present in as many as 15% of the population at risk—and duodenal ulcer, and any of these may present with complications such as gastrointestinal bleeding or perforation. Attempts to prevent NSAID-related gastropathy with H_2 -receptor blockers and sucralfate have been unsuccessful, though these agents remain useful for healing established ulcers once NSAID therapy is discontinued.

The mechanism of NSAID-induced mucosal damage is not completely understood. The suppression of mucosal prostaglandin production and a reduction of mucosal blood flow by NSAIDs are contributing factors, and the presence of gastric acid is required. Prostaglandins such as misoprostol, a synthetic prostaglandin E_2 analogue, have been investigated for their role in gastric mucosal protection, particularly against insults such as from taking NSAIDs. In low doses these agents have cytoprotective properties such as enhancing mucosal blood flow and gastric mucous production. In higher doses they can inhibit gastric acid secretion. In healthy subjects misoprostol use has been shown to prevent mucosal lesions induced by NSAIDs and aspirin. Even with doses below antisecretory levels, patients had lowered endoscopic scores of mucosal damage, suggesting cytoprotection by misoprostol. Notably, abdominal pain and other gastrointestinal symptoms were not reduced in these short-term studies.

Two recent trials show the clinical usefulness of misoprostol in arthritic patients on NSAID therapy. One trial enrolled patients with abdominal pain but without gastric ulcers on endoscopy and showed a significantly reduced incidence of gastric ulcer in the group treated with misoprostol. Because the overall incidence of gastric ulcer was high, the study was terminated for ethical reasons before statistically significant data could be collected on the effects on duodenal ulcers. In a second study, misoprostol therapy produced substantial regression of gastropathy in patients with rheumatoid arthritis who continued on aspirin therapy. No exacerbation of arthritic symptoms was noted in patients treated with misoprostol.

Unfortunately, none of these studies have shown any consistent benefit on abdominal symptoms; in fact, some have

shown worsened gastrointestinal symptoms in the misoprostol-treated patients. This is due in part to the side effects of the drug, which include diarrhea, dyspepsia, and abdominal pain, and may require reducing the dose from the recommended starting dose of 200 μ g four times a day to 100 μ g. Misoprostol also has uterotonic effects and may cause cramping, bleeding, or spontaneous abortion, necessitating extreme caution in prescribing to women of childbearing age and contraindicating its use in pregnancy.

Misoprostol therapy should certainly be considered for patients with disabling arthritis who need to continue on NSAID therapy despite a serious complication—such as gastric ulcer or gastrointestinal bleeding—from these agents. It may be indicated in symptomatic patients on NSAID therapy, particularly elderly or chronically ill persons, to prevent the development of gastric complications. Because its efficacy in reducing symptoms has not been shown, assessing any clinical benefit over the short term may be difficult, especially because many of these patients will not be followed up with endoscopy. The role of misoprostol therapy in high-risk asymptomatic patients without documented gastrointestinal complications bears further investigation. Its effects on the prevention and healing of duodenal ulcers need to be assessed. Finally, long-term studies are needed to evaluate the efficacy of misoprostol therapy in preventing more serious complications such as gastrointestinal bleeding and perforation and to identify the patient groups that may benefit from such therapy.

KRISHNA DAS, MD
Stanford, California

REFERENCES

- Fries JF, Miller SR, Spitz PW, et al: Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. *Gastroenterology* 1989; 96 (Pt 2 suppl):647-655
- Graham DY, Agrawal NM, Roth SH: Prevention of NSAID-induced gastric ulcer with misoprostol: Multicentre, double-blind, placebo-controlled trial. *Lancet* 1988; 2:1277-1280
- Roth S, Agrawal N, Mahowald M, et al: Misoprostol heals gastroduodenal injury in patients with rheumatoid arthritis receiving aspirin. *Arch Intern Med* 1989; 149:775-779
- Stern WR: Summary of the 33rd Meeting of the Food and Drug Administration's Gastrointestinal Drugs Advisory Committee, September 15-16, 1988. *Am J Gastroenterol* 1989; 84:351-353

Rheumatoid Arthritis and Methotrexate—A Renewed Partnership

METHOTREXATE was first used to treat hematologic malignant disorders in the late 1940s. It was later tried in rheumatic diseases with the assumption that the two groups of patients shared a similar pathophysiology. Because of the serious side effects associated with the earlier dosage regimens and the recognition of the dramatic effects of corticosteroids, its use was soon discarded. The modern application of methotrexate began in the 1960s when introduced in the treatment of psoriasis and dermatomyositis.

Since 1980 when an eight-year experience with the use of methotrexate to treat rheumatoid arthritis was described, several authors have published data supporting the relative safety and efficacy of its use in patients with this disorder. In 1988 the American College of Physicians published a "position paper" describing its use, and this year, after 45 years on the market, the Food and Drug Administration approved its use for the treatment of rheumatoid arthritis.

Methotrexate is a folic acid analogue. It inactivates intracellular enzymes, depleting the cell of reduced folates necessary for the formation of purines and pyrimidines and thus DNA. Its mechanism of action in rheumatoid arthritis is un-